IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al — Confirmation: 8927

Serial No.: 10/525,736 — Group Art Unit: 1617

Filed: June 6, 2005 — Examiner: SAMIRA JM, Jean-Louis

For: **PHARMACEUTICAL PRODUCTS AND COMPOSITIONS COMPRISING SPECIFIC ANTICHOLINERGICAGENTS, BETA-AGONISTS AND CORTICOSTEROIDS**

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Geena Malhotra, hereby declare and state that if called to testify I would be competent to testify to the following based on personal knowledge;

1. I am a co-inventor of the present application.

2. I am currently employed by the assignee of the present application as a Research Scientist.

3. I am familiar with the invention described in the above-identified application and with the Office Action dated May 5, 2009, mailed in connection with the prosecution of this application;

4. That I am aware that the Office Action of May 5, 2005 rejects certain claims as "unpatentable under 35 USC 103(a)" as "obvious" over the prior art;

5. That, the following experiments were conducted under my supervision and control in order to demonstrate the results of combining one, two and three active ingredients in formulations; with the results being attached in tabular form to this Declaration;

6. The experiments demonstrate that, as even compared to a single and double combinations of active ingredients, the claimed triple active combinations exhibit unexpectedly superior stability, delivering more of an effective dose over time than the comparative, and unclaimed, single and double active formulations listed;

7. That the triple combinations appear to defy the effect of agglomeration over time of the single and double comparative formulations, which agglomeration results in an enlarged particle size over time resulting in a decrease in fine particle dose upon administration as an aerosol which leads to a reduction in active penetration into the lungs, even though the comparative tests utilizes the same initial particle size formulation for each of the experiments;

8. These experiments demonstrate an unexpected property of, and result in, effectiveness of administration of the claimed triple combination of active ingredients as compared to single or double combinations of active ingredients;

9. That based upon the results of the experiments conducted, and upon my educational and work experience set forth above, these results are expected to be achieved with all the triple formulations claimed, including pharmaceutically acceptable salts and esters of the compounds exemplified, because each of the claimed combinations comprises an anticholinergic which absorbs moisture (i.e. Tiotropium, Oxitropium and Ipratropium and salts and esters thereof) and in each combination the anticholinergic is combined with both a beta-mimetic agent and a corticosteroid; the beta mimetic agent plus corticosteroid have been found to exhibit a masking effect on the absorption of water by the particular anticholinergics of the present invention, which absorption contributes to the agglomeration, and therefore the same results in terms of improved stability and reduced agglomeration are expected for all the claimed combinations.

10. Further the declarant sayeth not.

I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application or of any patent issuing thereon.

26/10/09

Date

G. Malhotra

Geena Malhotra

SUPPLEMENTARY DATA

1) Single Active Formulations

Tiotropium + HFA Propellant

Fine Particle Dose [FPD]:

	FPD	Particle size
Initial	16.67%	70% particles below 2.5%µ 26% particles between 2.5 µ-5 µ 4% particles between 5 µ-15 µ
1Month 40°C	10%	60% particles below 2.5%µ 25% particles between 2.5 µ-5 µ 15% particles between 5 µ-15 µ

Dose content Uniformity:

	Initial	1 Month 40°C
Average Dose	85%	64%

2) Double Active Formulations

Tiotropium + Formoterol+ HFA Propellant

Fine Particle Dose:

	FPD		Particle size
	Tiotropium	Formoterol	
Initial	34.67%	40.83%	95% particles below 2.5%µ 5% particles between 2.5 µ-7.5 µ
1 Month 40°C	28.88%	38.16%	75% particles below 2.5%µ 17% particles between 2.5 µ-5 µ 8% particles between 5 µ-10 µ

Dose content Uniformity:

	Initial		1 Month 40°C	
	Tiotropium	Formoterol	Tiotropium	Formoterol
Average Dose	68.67%	60.83%	73.77%	65.5%

3) Triple Active Formulations

(i) Tiotropium + Salmeterol + Fluticasone + HFA Propellant

Fine Particle Dose :

	FPD			Particle size
	Tiotropium	Salmeterol	Fluticasone	
Initial	49.55%	48.24%	45.08%	95% particles below 2.5%μ 5% particles between 2.5 μ-5 μ
6 Month 40°C	47.11%	45.12%	42.25%	95% particles below 2.5%μ 5% particles between 2.5 μ-5 μ

Dose content Uniformity:

	Initial			6 Month 40°C		
	Tiotropium	Salmeterol	Fluticasone	Tiotropium	Salmeterol	Fluticasone
Average Dose	89.77%	84.12%	86.35%	102.44%	93.72%	82.21%

(ii) Tiotropium + Ciclesonide + Formoterol + HFA Propellant

Fine Particle Dose:

	FPD			Particle size
	Tiotropium	Ciclesonide	Formoterol	
Initial	49.22%	44.4%	46.2%	95% particles below 2.5%μ 5% particles between 2.5 μ-5 μ
6 Month 40°C	48.66%	45.31%	47%	95% particles below 2.5%μ 5% particles between 2.5 μ-5 μ

Dose content Uniformity:

	Initial			6 Month 40°C		
	Tiotropium	Ciclesonide	Formoterol	Tiotropium	Ciclesonide	Formoterol
Average Dose	86.22%	84.33%	81.22%	85.67%	80.5%	82.33%

(iii) Tiotropium + Budesonide + Formoterol + HFA Propellant

Fine Particle Dose:

	FPD			Particle size
	Tiotropium	Budesonide	Formoterol	
Initial	45%	41.23%	37.16%	90% particles below 2.5%μ 10% particles between 2.5 μ-5 μ
6 Month 40°C	44.11%	39.22%	43.16%	90% particles below 2.5%μ 10% particles between 2.5 μ-5 μ

Dose content Uniformity:

	Initial			6 Month 40°C		
	Tiotropium	Budesonide	Formoterol	Tiotropium	Budesonide	Formoterol
Average Dose	94.67%	85.23%	87.33%	92%	84.38%	86.5%